

In The Claims

Kindly cancel claims 1 through 18, inclusive, without prejudice.

According to the new provisions of 37 C.F.R. 1.121, all pending claims (including claims 34 and 40; amended claims 33 and 39; and newly added claims 45-68) are provided in a rewritten and clean form as follows:

SAC 31

33 (thrice amended). A method for directly identifying a non-endogenous candidate compound as a compound having activity selected from the group consisting of inverse agonist activity and agonist activity to an endogenous G protein coupled cell surface receptor, wherein a location of expression of said receptor has been identified from a mammalian tissue source and has been correlated with at least one physiological function in a mammal, comprising the steps of:

- (a) selecting an endogenous G protein coupled cell surface receptor, wherein the endogenous ligand for said receptor has not been identified;
- (b) determining the location of expression of said receptor in a mammalian tissue source and correlating the expression location of said receptor with at least one mammalian physiological function of interest, wherein said location and said correlated physiological function are selected from the group consisting essentially of:

E1

Location:	Correlated Physiological Function:
1. gastrointestinal tract smooth muscle	1. motility of stomach and intestines
2. gastrointestinal tract ganglionic nerve fibers	2. motility of stomach and intestines
3. urinary tract smooth muscle	3. ureter function and urinary bladder function
4. salivary gland	4. salivary secretion
5. alpha cells of the pancreas	5. secretion of glucagon
6. beta cells of the pancreas	6. secretion of insulin
7. uterine smooth muscle	7. uterine contraction
8. heart muscle	8. contractility of heart muscle
9. vascular smooth muscle	9. contractility of smooth muscle
10. adipocytes	10. lipolysis
11. platelets	11. platelet aggregation in response to blood vessel injury
12. skeletal neuromuscular junction	12. skeletal muscle contractility
13. bronchial smooth muscle	13. respiration
14. nasal mucosal blood vessels	14. mucosa volume
15. trigone muscle of bladder and urethra	15. urinary outflow
16. chondrocytes	16. cartilage formation
17. ciliary body of the eye	17. aqueous humor production
18. thyroid	18. thyroid hormone secretion
19. mast cells	19. immediate hypersensitivity reactions

20. basophils	20. immediate hypersensitivity reactions
21. osteoblasts	21. bone remodeling
22. osteoclasts	22. bone remodeling
23. brain capillary endothelial cells	23. permeability of blood-brain barrier
24. T cells	24. immune response
25. B cells	25. immune response
26. kidney proximal tubular epithelial cells	26. organic acids exchange
27. neutrophils	27. immune response
28. eosinophils	28. immune response
29. monocytes	29. immune response
30. kidney late distal tubule	30. organic bases exchange
31. collecting duct principal cells	31. organic bases exchange
32. kidney granular juxtaglomerular cells	32. secretion of renin
33. peripheral postganglionic adrenergic neurons	33. sympathetic function
34. hepatocytes	34. synthesis of cholesterol and lipoprotein
35. gastrointestinal parietal cells	35. secretion of stomach acid
36. gastrointestinal superficial epithelial cells	36. secretion of cytoprotective factors, mucus and bicarbonate
37. epidermal cells	37. skin maintenance
38. bone marrow stem cells	38. erythropoiesis production
39. angle structures of the eye	39. aqueous humor outflow
40. uveoscleral structures of eye	40. aqueous humor outflow
41. suprachiasmatic nucleus	41. circadian rhythm
42. baroreceptors	42. blood pressure
43. basal ganglia	43. movement control
44. periaqueductal grey and dorsal horn of spinal cord	44. nociception
45. area postrema	45. vomiting
46. thalamus	46. sensorimotor processing and arousal
47. sensorimotor cerebral cortex	47. sensorimotor processing
48. spinal cord motor neurons	48. motor function control
49. dorsal root ganglion neurons	49. sensory information transmission
50. oligodendrocytes	50. neuron myelin sheath production
51. nucleus basalis	51. cognition and memory
52. nucleus accumbens	52. addictive cravings
53. lateral reticular formation of medulla	53. vomiting
54. hypothalamic neurons containing growth hormone releasing factor (GHRH)	54. secretion of GHRH
55. hypothalamic neurons containing somatostatin	55. secretion of somatostatin
56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH)	56. secretion of TRH
57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH)	57. secretion of GnRH
58. hypothalamic neurons containing corticotropin releasing factor (CRF)	58. secretion of CRF


 Sect 3
 Cont

59. anterior pituitary somatotropes	59. secretion of growth hormone
60. anterior pituitary lactotropes	60. secretion of prolactin
61. anterior pituitary gonadotropes	61. secretion of luteinizing hormone
62. anterior pituitary gonadotropes	62. secretion of follicle stimulating hormone
63. anterior pituitary corticotropes	63. secretion of adrenocorticotropic hormone
64. leydig cells of the testes	64. secretion of testosterone
65. sertoli cells of the testes	65. spermatogenesis
66. granulosa cells of the ovary	66. synthesis of estrogen
67. theca cells of the ovary	67. synthesis of estrogen
68. synovium	68. joint function
69. amygdala	69. modulation of emotion
70. pineal gland	70. regulation of circadian rhythm
71. nucleus of the solitary tract	71. cardiovascular regulation
72. caudal ventrolateral medulla	72. cardiovascular regulation
73. rostral ventrolateral medulla	73. vasopressor activity
74. parabrachial nucleus	74. taste aversion response and nociceptive response
75. entorhinal cortex	75. cognition
76. pyriform cortex	76. cognition
77. temporal cortex	77. memory acquisition
78. frontal cortex	78. regulation of emotional response and memory acquisition
79. parietal cortex	79. visual acuity, touch perception, and voluntary movement
80. occipital cortex	80. visual acuity
81. hippocampus	81. learning and memory
82. dentate gyrus	82. learning and memory
83. midbrain reticular formation	83. arousal
84. supraoptic nucleus of the hypothalamus	84. reproductive functions
85. magnocellular of the hypothalamus	85. modulation of stress, blood pressure and lactation
86. parvocellular neurons of the hypothalamus	86. metabolism
87. arcuate nucleus of the hypothalamus	87. release of pituitary hormones
88. trigeminal area	88. cerebral vessel dilation and blood pressure
89. cerebral blood vessels	89. cerebral vessel dilation
90. brain stem	90. breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature
91. ventral lamina terminalis	91. blood pressure
92. vagus nerve	92. blood pressure and heart rate
93. nucleus of the solitary tract	93. blood pressure
94. adrenal medulla	94. catecholamine response to stress
95. adrenal cortex	95. stress-induced corticosterone release
96. locus coeruleus	96. arousal and response to stress

Sub
 T
 Cont
 E

97. substantia nigra	97. control of body movement
98. ventral tegmental area	98. control of body movement
99. olfactory bulb	99. odor perception
100. median eminence of hypothalamus	100. pituitary function
101. raphe nuclei	101. sleep and arousal
102. habenula	102. sexual activity
103. cerebellum	103. control of body movement
104. posterior hypothalamus	104. intestinal motility and blood pressure
105. dorsal medulla	105. blood pressure
106. lateral hypothalamus	106. food intake and stomach acid secretion
107. rostral hypothalamus	107. heart rate
108. pontine-medullary reticular formation	108. respiration and heart rate
109. medulla	109. respiration and heart rate
110. mesencephalon	110. heart rate
111. ventral hypothalamus	111. response to stress
112. paraventricular nucleus of hypothalamus	112. response to stress
113. preoptic area of hypothalamus	113. sexual activity
114. mammillary region	114. food intake
115. perifornical area of hypothalamus	115. food intake
116. ventromedial hypothalamus	116. food intake
117. pons/reticular formation	117. arousal and wakefulness
118. septum	118. emotional control
119. pedunculopontine tegmental nucleus	119. arousal
120. astrocytes	120. neuronal metabolism
121. microglia	121. response to neuronal injury
122. choroid plexus	122. production of cerebrospinal fluid
123. Schwann cells	123. myelination of peripheral nerves
124. endoneurium	124. production of connective tissue nerve sheath
125. lateral spinothalamic pathway	125. response to pain and temperature stimuli
126. ventral spinothalamic pathway	126. touch sensation
127. dorsal column-medial lemniscal pathway	127. touch sensation
128. free nerve endings	128. response to pain and temperature
129. hair follicle endings	129. touch sensation
130. Krause's end-bulb	130. temperature sensation
131. Meissner's corpuscles	131. touch-pressure sensation
132. Merkel's disk	132. touch-pressure sensation
133. Pacinian corpuscle	133. touch-pressure sensation
134. Ruffini's corpuscle	134. temperature sensation
135. retina	135. visual acuity
136. parathyroid gland	136. calcium balance
137. placenta	137. placental activity
138. skeletal muscle fibers	138. muscle contraction

Sub
 Chg
 Cont

139. copora cavernosum	139. genital vasodilation
140. corticospinal tract	140. movement control
141. motor cerebral cortex	141. movement control
142. postganglionic neurons	142. control of blood pressure and adrenal activity
143. intramural ganglion	143. distal colon peristalsis
144. hypogastric plexus	144. control of urethral and anal sphincters
145. pelvic plexus	145. genital vasodilatation and penile erection
146. vesical plexus	146. urinary bladder control
147. celiac plexus	147. intestinal peristolisis

- Sub G1
Cont*
- (c) subjecting said receptor to constitutive receptor activation to establish a non-endogenous constitutively activated G protein coupled cell surface receptor;
 - (d) contacting a non-endogenous candidate compound with said non-endogenous constitutively activated G protein coupled cell surface receptor of step (c);
 - (e) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous candidate compound has inverse agonist activity or agonist activity to said receptor of step (c); and
 - (f) directly identifying a non-endogenous candidate compound of step (e) having inverse agonist activity as an inverse agonist to said receptor of step (c), or having agonist activity as an agonist to said receptor of step (c);
 - (g) selecting an inverse agonist to reduce a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a), or selecting an agonist to enhance a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a); and
 - (h) contacting said inverse agonist with a mammal comprising said receptor of step (a) and confirming that said inverse agonist reduces said selected physiological function, or contacting said agonist with a mammal comprising said receptor of step (a) and confirming that said agonist enhances said selected physiological function

*E
Cont*

wherein said directly identified non-endogenous candidate compound of step (f) was not, prior to such direct identification, indirectly identified as an agonist or antagonist to said endogenous G protein coupled cell surface receptor.

- Sub G1*
34. The method of claim 33 wherein the candidate compound is directly identified as having inverse activity at said receptor.

Sub 32

39 (thrice amended). A method for directly identifying a non-endogenous candidate compound as a compound having activity selected from the group consisting of inverse agonist activity and agonist activity to an endogenous constitutively activated G protein coupled cell surface receptor, wherein a location of expression of said receptor has been identified from a mammalian tissue source, comprising the steps of:

- (a) selecting an endogenous constitutively activated G protein coupled cell surface receptor, wherein the ligand for said receptor has not been identified;
- (b) determining the location of expression of said receptor in a mammalian tissue source and correlating the expression location of said receptor with at least one mammalian physiological function of interest, wherein said location and said correlated physiological function are selected from group consisting essentially of:



Location:	Correlated Physiological Function:
1. gastrointestinal tract smooth muscle	1. motility of stomach and intestines
2. gastrointestinal tract ganglionic nerve fibers	2. motility of stomach and intestines
3. urinary tract smooth muscle	3. ureter function and urinary bladder function
4. salivary gland	4. salivary secretion
5. alpha cells of the pancreas	5. secretion of glucagon
6. beta cells of the pancreas	6. secretion of insulin
7. uterine smooth muscle	7. uterine contraction
8. heart muscle	8. contractility of heart muscle
9. vascular smooth muscle	9. contractility of smooth muscle
10. adipocytes	10. lipolysis
11. platelets	11. platelet aggregation in response to blood vessel injury
12. skeletal neuromuscular junction	12. skeletal muscle contractility
13. bronchial smooth muscle	13. respiration
14. nasal mucosal blood vessels	14. mucosa volume
15. trigone muscle of bladder and urethra	15. urinary outflow
16. chondrocytes	16. cartilage formation
17. ciliary body of the eye	17. aqueous humor production
18. thyroid	18. thyroid hormone secretion
19. mast cells	19. immediate hypersensitivity reactions
20. basophils	20. immediate hypersensitivity reactions
21. osteoblasts	21. bone remodeling
22. osteoclasts	22. bone remodeling
23. brain capillary endothelial cells	23. permeability of blood-brain barrier
24. T cells	24. immune response
25. B cells	25. immune response
26. kidney proximal tubular epithelial cells	26. organic acids exchange
27. neutrophils	27. immune response
28. eosinophils	28. immune response
29. monocytes	29. immune response
30. kidney late distal tubule	30. organic bases exchange

31. collecting duct principal cells	31. organic bases exchange
32. kidney granular juxtaglomerular cells	32. secretion of renin
33. peripheral postganglionic adrenergic neurons	33. sympathetic function
34. hepatocytes	34. synthesis of cholesterol and lipoprotein
35. gastrointestinal parietal cells	35. secretion of stomach acid
36. gastrointestinal superficial epithelial cells	36. secretion of cytoprotective factors, mucus and bicarbonate
37. epidermal cells	37. skin maintenance
38. bone marrow stem cells	38. erythropoiesis production
39. angle structures of the eye	39. aqueous humor outflow
40. uveoscleral structures of eye	40. aqueous humor outflow
41. suprachiasmatic nucleus	41. circadian rhythm
42. baroreceptors	42. blood pressure
43. basal ganglia	43. movement control
44. periaqueductal grey and dorsal horn of spinal cord	44. nociception
45. area postrema	45. vomiting
46. thalamus	46. sensorimotor processing and arousal
47. sensorimotor cerebral cortex	47. sensorimotor processing
48. spinal cord motor neurons	48. motor function control
49. dorsal root ganglion neurons	49. sensory information transmission
50. oligodendrocytes	50. neuron myelin sheath production
51. nucleus basalis	51. cognition and memory
52. nucleus accumbens	52. addictive cravings
53. lateral reticular formation of medulla	53. vomiting
54. hypothalamic neurons containing growth hormone releasing factor (GHRH)	54. secretion of GHRH
55. hypothalamic neurons containing somatostatin	55. secretion of somatostatin
56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH)	56. secretion of TRH
57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH)	57. secretion of GnRH
58. hypothalamic neurons containing corticotropin releasing factor (CRF)	58. secretion of CRF
59. anterior pituitary somatotropes	59. secretion of growth hormone
60. anterior pituitary lactotropes	60. secretion of prolactin
61. anterior pituitary gonadotropes	61. secretion of luteinizing hormone
62. anterior pituitary gonadotropes	62. secretion of follicle stimulating hormone
63. anterior pituitary corticotropes	63. secretion of adrenocorticotropic hormone
64. leydig cells of the testes	64. secretion of testosterone
65. sertoli cells of the testes	65. spermatogenesis
66. granulosa cells of the ovary	66. synthesis of estrogen
67. theca cells of the ovary	67. synthesis of estrogen
68. synovium	68. joint function

E2
cont
Sub
32
unt

69. amygdala	69. modulation of emotion
70. pineal gland	70. regulation of circadian rhythm
71. nucleus of the solitary tract	71. cardiovascular regulation
72. caudal ventrolateral medulla	72. cardiovascular regulation
73. rostral ventrolateral medulla	73. vasopressor activity
74. parabrachial nucleus	74. taste aversion response and nociceptive response
75. entorhinal cortex	75. cognition
76. pyriform cortex	76. cognition
77. temporal cortex	77. memory acquisition
78. frontal cortex	78. regulation of emotional response and memory acquisition
79. parietal cortex	79. visual acuity, touch perception, and voluntary movement
80. occipital cortex	80. visual acuity
81. hippocampus	81. learning and memory
82. dentate gyrus	82. learning and memory
83. midbrain reticular formation	83. arousal
84. supraoptic nucleus of the hypothalamus	84. reproductive functions
85. magnocellular of the hypothalamus	85. modulation of stress, blood pressure and lactation
86. parvocellular neurons of the hypothalamus	86. metabolism
87. arcuate nucleus of the hypothalamus	87. release of pituitary hormones
88. trigeminal area	88. cerebral vessel dilation and blood pressure
89. cerebral blood vessels	89. cerebral vessel dilation
90. brain stem	90. breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature
91. ventral lamina terminalis	91. blood pressure
92. vagus nerve	92. blood pressure and heart rate
93. nucleus of the solitary tract	93. blood pressure
94. adrenal medulla	94. catecholamine response to stress
95. adrenal cortex	95. stress-induced corticosterone release
96. locus coeruleus	96. arousal and response to stress
97. substantia nigra	97. control of body movement
98. ventral tegmental area	98. control of body movement
99. olfactory bulb	99. odor perception
100. median eminence of hypothalamus	100. pituitary function
101. raphe nuclei	101. sleep and arousal
102. habenula	102. sexual activity
103. cerebellum	103. control of body movement
104. posterior hypothalamus	104. intestinal motility and blood pressure
105. dorsal medulla	105. blood pressure
106. lateral hypothalamus	106. food intake and stomach acid secretion

Sub
32
cont
E2
cont

107. rostral hypothalamus	107. heart rate
108. pontine-medullary reticular formation	108. respiration and heart rate
109. medulla	109. respiration and heart rate
110. mesencephalon	110. heart rate
111. ventral hypothalamus	111. response to stress
112. paraventricular nucleus of hypothalamus	112. response to stress
113. preoptic area of hypothalamus	113. sexual activity
114. mammillary region	114. food intake
115. perifornical area of hypothalamus	115. food intake
116. ventromedial hypothalamus	116. food intake
117. pons/reticular formation	117. arousal and wakefulness
118. septum	118. emotional control
119. pedunculopontine tegmental nucleus	119. arousal
120. astrocytes	120. neuronal metabolism
121. microglia	121. response to neuronal injury
122. choroid plexus	122. production of cerebrospinal fluid
123. Schwann cells	123. myelination of peripheral nerves
124. endoneurium	124. production of connective tissue nerve sheath
125. lateral spinothalamic pathway	125. response to pain and temperature stimuli
126. ventral spinothalamic pathway	126. touch sensation
127. dorsal column-medial lemniscal pathway	127. touch sensation
128. free nerve endings	128. response to pain and temperature
129. hair follicle endings	129. touch sensation
130. Krause's end-bulb	130. temperature sensation
131. Meissner's corpuscles	131. touch-pressure sensation
132. Merkel's disk	132. touch-pressure sensation
133. Pacinian corpuscle	133. touch-pressure sensation
134. Ruffini's corpuscle	134. temperature sensation
135. retina	135. visual acuity
136. parathyroid gland	136. calcium balance
137. placenta	137. placental activity
138. skeletal muscle fibers	138. muscle contraction
139. copora cavernosum	139. genital vasodilation
140. corticospinal tract	140. movement control
141. motor cerebral cortex	141. movement control
142. postganglionic neurons	142. control of blood pressure and adrenal activity
143. intramural ganglion	143. distal colon peristalsis
144. hypogastric plexus	144. control of urethral and anal sphincters
145. pelvic plexus	145. genital vasodilatation and penile erection
146. vesical plexus	146. urinary bladder control
147. celiac plexus	147. intestinal peristolis

Sub
 3/2
 cont
 E 2
 cont

- Sub G2*
- (c) contacting a non-endogenous candidate compound with said endogenous constitutively activated G protein coupled cell surface receptor of step (a);
- (d) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous candidate compound has inverse agonist activity or agonist activity to said receptor of step (a); and
- (e) directly identifying a non-endogenous candidate compound of step (d) having inverse agonist activity as an inverse agonist to said receptor of step (a), or having agonist activity as an agonist to said receptor of step (a);
- (f) selecting an inverse agonist to reduce a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a), or selecting an agonist to enhance a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a); and
- (g) contacting said inverse agonist with a mammal comprising said receptor of step (a) and confirming that said inverse agonist reduces said selected physiological function, or contacting said agonist with a mammal comprising said receptor of step (a) and confirming that said agonist enhances said selected physiological function
- E2 Cont*

wherein said directly identified non-endogenous candidate compound of step (e) was not, prior to such direct identification, indirectly identified as an agonist or antagonist to said receptor.

- Sub G2*
40. The method of claim 39 wherein the candidate compound is directly identified as having inverse activity at said receptor.

- Sub G3*
- 45 (New). The method of claim 33 wherein the third intracellular loop of the receptor of step (b) comprises the following sequence:



wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

- E-3*
- 46 (New). The method of claim 45 wherein X1 is glycine.
- 47 (New). The method of claim 45 wherein X1 is lysine.
- 48 (New). The method of claim 45 wherein Hy is alanine.
- 49 (New). The method of claim 45 wherein X2 is lysine.
- 50 (New). The method of claim 45 wherein X2 is arginine.
- 51 (New). The method of claim 45 wherein X2 is glutamic acid.

52 (New). The method of claim 33 wherein the second intracellular loop of the receptor of step (b) comprises the following sequence:

XRY

Sub SA
wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

53 (New). The method of claim 39 wherein the third intracellular loop of the receptor of step (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

54 (New). The method of claim 53 wherein X1 is glycine.

55 (New). The method of claim 53 wherein X1 is lysine.

56 (New). The method of claim 53 wherein Hy is alanine.

57 (New). The method of claim 53 wherein X2 is lysine.

58 (New). The method of claim 53 wherein X2 is arginine.

59 (New). The method of claim 53 wherein X2 is glutamic acid.

60 (New). The method of claim 39 wherein the second intracellular loop of the receptor of step (a) comprises the following sequence:

XRY

Sub 65
wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

b
Cont
61 (New). The method of claim 45 wherein the sequence X1BBHyX2 is an endogenous sequence.

62 (New). The method of claim 52 wherein the sequence XRY is an endogenous sequence.

63 (New). The method of claim 33 wherein said mammal of step (h) is a human.

64 (New). The method of claim 39 wherein said mammal of step (i) is a human.

65 (New). The method of claim 33 wherein said mammal of step (h) is a non-human.

66 (New). The method of claim 39 wherein said mammal of step (i) is a non-human.

67 (New). The method of claim 33 wherein said physiological function of step (b) is an abnormal physiological function.

68 (New). The method of claim 39 wherein said physiological function of step (c) is an abnormal physiological function.

*Sub 66
cont*

According to 37 C.F.R. 1.121, a marked up version of amended claims 33 and 39, and newly added claims 45 through 68 are as follows:

33 (thrice amended). A method for directly identifying a non-endogenous candidate compound as a compound having activity selected from the group consisting of inverse agonist activity and agonist activity to [a non-] an endogenous [constitutively activated] G protein coupled cell surface [orphan] receptor, wherein a location of expression of said receptor has been identified from a mammalian tissue source and has been correlated with at least one physiological function in a mammal, comprising the steps of:

- (b) selecting an endogenous G protein coupled cell surface receptor, wherein the endogenous ligand for said receptor has not been identified;
- (b) determining the location of expression of said receptor in a mammalian tissue source and correlating the expression location of said receptor with at least one mammalian physiological function of interest, wherein said location and said correlated physiological function are selected from the group consisting essentially of:

Location:	Correlated Physiological Function:
1. gastrointestinal tract smooth muscle	1. motility of stomach and intestines
2. gastrointestinal tract ganglionic nerve fibers	2. motility of stomach and intestines
3. urinary tract smooth muscle	3. ureter function and urinary bladder function
4. salivary gland	4. salivary secretion
5. alpha cells of the pancreas	5. secretion of glucagon
6. beta cells of the pancreas	6. secretion of insulin
7. uterine smooth muscle	7. uterine contraction
8. heart muscle	8. contractility of heart muscle
9. vascular smooth muscle	9. contractility of smooth muscle
10. adipocytes	10. lipolysis
11. platelets	11. platelet aggregation in response to blood vessel injury
12. skeletal neuromuscular junction	12. skeletal muscle contractility
13. bronchial smooth muscle	13. respiration
14. nasal mucosal blood vessels	14. mucosa volume
15. trigone muscle of bladder and urethra	15. urinary outflow
16. chondrocytes	16. cartilage formation
17. ciliary body of the eye	17. aqueous humor production
18. thyroid	18. thyroid hormone secretion
19. mast cells	19. immediate hypersensitivity reactions
20. basophils	20. immediate hypersensitivity reactions
21. osteoblasts	21. bone remodeling
22. osteoclasts	22. bone remodeling
23. brain capillary endothelial cells	23. permeability of blood-brain barrier

24. T cells	24. immune response
25. B cells	25. immune response
26. kidney proximal tubular epithelial cells	26. organic acids exchange
27. neutrophils	27. immune response
28. eosinophils	28. immune response
29. monocytes	29. immune response
30. kidney late distal tubule	30. organic bases exchange
31. collecting duct principal cells	31. organic bases exchange
32. kidney granular juxtaglomerular cells	32. secretion of renin
33. peripheral postganglionic adrenergic neurons	33. sympathetic function
34. hepatocytes	34. synthesis of cholesterol and lipoprotein
35. gastrointestinal parietal cells	35. secretion of stomach acid
36. gastrointestinal superficial epithelial cells	36. secretion of cytoprotective factors, mucus and bicarbonate
37. epidermal cells	37. skin maintenance
38. bone marrow stem cells	38. erythropoiesis production
39. angle structures of the eye	39. aqueous humor outflow
40. uveoscleral structures of eye	40. aqueous humor outflow
41. suprachiasmatic nucleus	41. circadian rhythm
42. baroreceptors	42. blood pressure
43. basal ganglia	43. movement control
44. periaqueductal grey and dorsal horn of spinal cord	44. nociception
45. area postrema	45. vomiting
46. thalamus	46. sensorimotor processing and arousal
47. sensorimotor cerebral cortex	47. sensorimotor processing
48. spinal cord motor neurons	48. motor function control
49. dorsal root ganglion neurons	49. sensory information transmission
50. oligodendrocytes	50. neuron myelin sheath production
51. nucleus basalis	51. cognition and memory
52. nucleus accumbens	52. addictive cravings
53. lateral reticular formation of medulla	53. vomiting
54. hypothalamic neurons containing growth hormone releasing factor (GHRH)	54. secretion of GHRH
55. hypothalamic neurons containing somatostatin	55. secretion of somatostatin
56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH)	56. secretion of TRH
57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH)	57. secretion of GnRH
58. hypothalamic neurons containing corticotropin releasing factor (CRF)	58. secretion of CRF
59. anterior pituitary somatotropes	59. secretion of growth hormone
60. anterior pituitary lactotropes	60. secretion of prolactin
61. anterior pituitary gonadotropes	61. secretion of luteinizing hormone

62. anterior pituitary gonadotropes	62. secretion of follicle stimulating hormone
63. anterior pituitary corticotropes	63. secretion of adrenocorticotropic hormone
64. leydig cells of the testes	64. secretion of testosterone
65. sertoli cells of the testes	65. spermatogenesis
66. granulosa cells of the ovary	66. synthesis of estrogen
67. theca cells of the ovary	67. synthesis of estrogen
68. synovium	68. joint function
69. amygdala	69. modulation of emotion
70. pineal gland	70. regulation of circadian rhythm
71. nucleus of the solitary tract	71. cardiovascular regulation
72. caudal ventrolateral medulla	72. cardiovascular regulation
73. rostral ventrolateral medulla	73. vasopressor activity
74. parabrachial nucleus	74. taste aversion response and nociceptive response
75. entorhinal cortex	75. cognition
76. pyriform cortex	76. cognition
77. temporal cortex	77. memory acquisition
78. frontal cortex	78. regulation of emotional response and memory acquisition
79. parietal cortex	79. visual acuity, touch perception, and voluntary movement
80. occipital cortex	80. visual acuity
81. hippocampus	81. learning and memory
82. dentate gyrus	82. learning and memory
83. midbrain reticular formation	83. arousal
84. supraoptic nucleus of the hypothalamus	84. reproductive functions
85. magnocellular of the hypothalamus	85. modulation of stress, blood pressure and lactation
86. parvocellular neurons of the hypothalamus	86. metabolism
87. arcuate nucleus of the hypothalamus	87. release of pituitary hormones
88. trigeminal area	88. cerebral vessel dilation and blood pressure
89. cerebral blood vessels	89. cerebral vessel dilation
90. brain stem	90. breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature
91. ventral lamina terminalis	91. blood pressure
92. vagus nerve	92. blood pressure and heart rate
93. nucleus of the solitary tract	93. blood pressure
94. adrenal medulla	94. catecholamine response to stress
95. adrenal cortex	95. stress-induced corticosterone release
96. locus coeruleus	96. arousal and response to stress
97. substantia nigra	97. control of body movement
98. ventral tegmental area	98. control of body movement

99. olfactory bulb	99. odor perception
100. median eminence of hypothalamus	100. pituitary function
101. raphe nuclei	101. sleep and arousal
102. habenula	102. sexual activity
103. cerebellum	103. control of body movement
104. posterior hypothalamus	104. intestinal motility and blood pressure
105. dorsal medulla	105. blood pressure
106. lateral hypothalamus	106. food intake and stomach acid secretion
107. rostral hypothalamus	107. heart rate
108. pontine-medullary reticular formation	108. respiration and heart rate
109. medulla	109. respiration and heart rate
110. mesencephalon	110. heart rate
111. ventral hypothalamus	111. response to stress
112. paraventricular nucleus of hypothalamus	112. response to stress
113. preoptic area of hypothalamus	113. sexual activity
114. mammillary region	114. food intake
115. perifornical area of hypothalamus	115. food intake
116. ventromedial hypothalamus	116. food intake
117. pons/reticular formation	117. arousal and wakefulness
118. septum	118. emotional control
119. pedunculopontine tegmental nucleus	119. arousal
120. astrocytes	120. neuronal metabolism
121. microglia	121. response to neuronal injury
122. choroid plexus	122. production of cerebrospinal fluid
123. Schwann cells	123. myelination of peripheral nerves
124. endoneurium	124. production of connective tissue nerve sheath
125. lateral spinothalamic pathway	125. response to pain and temperature stimuli
126. ventral spinothalamic pathway	126. touch sensation
127. dorsal column-medial lemniscal pathway	127. touch sensation
128. free nerve endings	128. response to pain and temperature
129. hair follicle endings	129. touch sensation
130. Krause's end-bulb	130. temperature sensation
131. Meissner's corpuscles	131. touch-pressure sensation
132. Merkel's disk	132. touch-pressure sensation
133. Pacinian corpuscle	133. touch-pressure sensation
134. Ruffini's corpuscle	134. temperature sensation
135. retina	135. visual acuity
136. parathyroid gland	136. calcium balance
137. placenta	137. placental activity
138. skeletal muscle fibers	138. muscle contraction
139. copora cavernosum	139. genital vasodilation
140. corticospinal tract	140. movement control

141. motor cerebral cortex	141. movement control
142. postganglionic neurons	142. control of blood pressure and adrenal activity
143. intramural ganglion	143. distal colon peristalsis
144. hypogastric plexus	144. control of urethral and anal sphincters
145. pelvic plexus	145. genital vasodilatation and penile erection
146. vesical plexus	146. urinary bladder control
147. celiac plexus	147. intestinal peristolis

- (c) subjecting said receptor to constitutive receptor activation to establish a non-endogenous constitutively activated G protein coupled cell surface receptor;
- (d) contacting a non-endogenous candidate compound with [a] said non-endogenous constitutively activated G protein coupled cell surface [orphan] receptor of step (c);
- (e) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous candidate compound has inverse agonist activity or agonist activity to said receptor of step (c); and
- (f) directly identifying a non-endogenous candidate compound of step [(b)] (e) having inverse agonist activity as an inverse agonist to said receptor of step (c), or having agonist activity as an agonist to said receptor of step (c) [.];
- (g) selecting an inverse agonist to reduce a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a), or selecting an agonist to enhance a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a); and
- (h) contacting said inverse agonist with a mammal comprising said receptor of step (a) and confirming that said inverse agonist reduces said selected physiological function, or contacting said agonist with a mammal comprising said receptor of step (a) and confirming that said agonist enhances said selected physiological function

wherein said directly identified non-endogenous candidate compound of step (f) was not, prior to such direct identification, indirectly identified as an agonist or antagonist to said endogenous G protein coupled cell surface receptor.

39 (thrice amended). A method for directly identifying a non-endogenous candidate compound as a compound having activity selected from the group consisting of inverse agonist activity and agonist activity to an endogenous constitutively activated G protein coupled cell surface [orphan] receptor, wherein a location of expression of said receptor has been identified from a mammalian tissue source, comprising the steps of:

- (a) selecting an endogenous constitutively activated G protein coupled cell surface receptor, wherein the ligand for said receptor has not been identified;

- (b) determining the location of expression of said receptor in a mammalian tissue source and correlating the expression location of said receptor with at least one mammalian physiological function of interest, wherein said location and said correlated physiological function are selected from group consisting essentially of:

Location:	Correlated Physiological Function:
1. gastrointestinal tract smooth muscle	1. motility of stomach and intestines
2. gastrointestinal tract ganglionic nerve fibers	2. motility of stomach and intestines
3. urinary tract smooth muscle	3. ureter function and urinary bladder function
4. salivary gland	4. salivary secretion
5. alpha cells of the pancreas	5. secretion of glucagon
6. beta cells of the pancreas	6. secretion of insulin
7. uterine smooth muscle	7. uterine contraction
8. heart muscle	8. contractility of heart muscle
9. vascular smooth muscle	9. contractility of smooth muscle
10. adipocytes	10. lipolysis
11. platelets	11. platelet aggregation in response to blood vessel injury
12. skeletal neuromuscular junction	12. skeletal muscle contractility
13. bronchial smooth muscle	13. respiration
14. nasal mucosal blood vessels	14. mucosa volume
15. trigone muscle of bladder and urethra	15. urinary outflow
16. chondrocytes	16. cartilage formation
17. ciliary body of the eye	17. aqueous humor production
18. thyroid	18. thyroid hormone secretion
19. mast cells	19. immediate hypersensitivity reactions
20. basophils	20. immediate hypersensitivity reactions
21. osteoblasts	21. bone remodeling
22. osteoclasts	22. bone remodeling
23. brain capillary endothelial cells	23. permeability of blood-brain barrier
24. T cells	24. immune response
25. B cells	25. immune response
26. kidney proximal tubular epithelial cells	26. organic acids exchange
27. neutrophils	27. immune response
28. eosinophils	28. immune response
29. monocytes	29. immune response
30. kidney late distal tubule	30. organic bases exchange
31. collecting duct principal cells	31. organic bases exchange
32. kidney granular juxtaglomerular cells	32. secretion of renin
33. peripheral postganglionic adrenergic	33. sympathetic function

34. hepatocytes	34. synthesis of cholesterol and lipoprotein
35. gastrointestinal parietal cells	35. secretion of stomach acid
36. gastrointestinal superficial epithelial cells	36. secretion of cytoprotective factors, mucus and bicarbonate
37. epidermal cells	37. skin maintenance
38. bone marrow stem cells	38. erythropoiesis production
39. angle structures of the eye	39. aqueous humor outflow
40. uveoscleral structures of eye	40. aqueous humor outflow
41. suprachiasmatic nucleus	41. circadian rhythm
42. baroreceptors	42. blood pressure
43. basal ganglia	43. movement control
44. periaqueductal grey and dorsal horn of spinal cord	44. nociception
45. area postrema	45. vomiting
46. thalamus	46. sensorimotor processing and arousal
47. sensorimotor cerebral cortex	47. sensorimotor processing
48. spinal cord motor neurons	48. motor function control
49. dorsal root ganglion neurons	49. sensory information transmission
50. oligodendrocytes	50. neuron myelin sheath production
51. nucleus basalis	51. cognition and memory
52. nucleus accumbens	52. addictive cravings
53. lateral reticular formation of medulla	53. vomiting
54. hypothalamic neurons containing growth hormone releasing factor (GHRH)	54. secretion of GHRH
55. hypothalamic neurons containing somatostatin	55. secretion of somatostatin
56. hypothalamic neurons containing thyrotropin-releasing hormone (TRH)	56. secretion of TRH
57. hypothalamic neurons containing gonadotropin releasing hormone (GnRH)	57. secretion of GnRH
58. hypothalamic neurons containing corticotropin releasing factor (CRF)	58. secretion of CRF
59. anterior pituitary somatotropes	59. secretion of growth hormone
60. anterior pituitary lactotropes	60. secretion of prolactin
61. anterior pituitary gonadotropes	61. secretion of luteinizing hormone
62. anterior pituitary gonadotropes	62. secretion of follicle stimulating hormone
63. anterior pituitary corticotropes	63. secretion of adrenocorticotropic hormone
64. leydig cells of the testes	64. secretion of testosterone
65. sertoli cells of the testes	65. spermatogenesis
66. granulosa cells of the ovary	66. synthesis of estrogen
67. theca cells of the ovary	67. synthesis of estrogen
68. synovium	68. joint function
69. amygdala	69. modulation of emotion
70. pineal gland	70. regulation of circadian rhythm
71. nucleus of the solitary tract	71. cardiovascular regulation
72. caudal ventrolateral medulla	72. cardiovascular regulation

73. rostral ventrolateral medulla	73. vasopressor activity
74. parabrachial nucleus	74. taste aversion response and nociceptive response
75. entorhinal cortex	75. cognition
76. pyriform cortex	76. cognition
77. temporal cortex	77. memory acquisition
78. frontal cortex	78. regulation of emotional response and memory acquisition
79. parietal cortex	79. visual acuity, touch perception, and voluntary movement
80. occipital cortex	80. visual acuity
81. hippocampus	81. learning and memory
82. dentate gyrus	82. learning and memory
83. midbrain reticular formation	83. arousal
84. supraoptic nucleus of the hypothalamus	84. reproductive functions
85. magnocellular of the hypothalamus	85. modulation of stress, blood pressure and lactation
86. parvocellular neurons of the hypothalamus	86. metabolism
87. arcuate nucleus of the hypothalamus	87. release of pituitary hormones
88. trigeminal area	88. cerebral vessel dilation and blood pressure
89. cerebral blood vessels	89. cerebral vessel dilation
90. brain stem	90. breathing, heart rate, startle responses, sweating, blood pressure, digestion and body temperature
91. ventral lamina terminalis	91. blood pressure
92. vagus nerve	92. blood pressure and heart rate
93. nucleus of the solitary tract	93. blood pressure
94. adrenal medulla	94. catecholamine response to stress
95. adrenal cortex	95. stress-induced corticosterone release
96. locus coeruleus	96. arousal and response to stress
97. substantia nigra	97. control of body movement
98. ventral tegmental area	98. control of body movement
99. olfactory bulb	99. odor perception
100. median eminence of hypothalamus	100. pituitary function
101. raphe nuclei	101. sleep and arousal
102. habenula	102. sexual activity
103. cerebellum	103. control of body movement
104. posterior hypothalamus	104. intestinal motility and blood pressure
105. dorsal medulla	105. blood pressure
106. lateral hypothalamus	106. food intake and stomach acid secretion
107. rostral hypothalamus	107. heart rate
108. pontine-medullary reticular formation	108. respiration and heart rate
109. medulla	109. respiration and heart rate

110. mesencephalon	110. heart rate
111. ventral hypothalamus	111. response to stress
112. paraventricular nucleus of hypothalamus	112. response to stress
113. preoptic area of hypothalamus	113. sexual activity
114. mammillary region	114. food intake
115. perifornical area of hypothalamus	115. food intake
116. ventromedial hypothalamus	116. food intake
117. pons/reticular formation	117. arousal and wakefulness
118. septum	118. emotional control
119. pedunculopontine tegmental nucleus	119. arousal
120. astrocytes	120. neuronal metabolism
121. microglia	121. response to neuronal injury
122. choroid plexus	122. production of cerebrospinal fluid
123. Schwann cells	123. myelination of peripheral nerves
124. endoneurium	124. production of connective tissue nerve sheath
125. lateral spinothalamic pathway	125. response to pain and temperature stimuli
126. ventral spinothalamic pathway	126. touch sensation
127. dorsal column-medial lemniscal pathway	127. touch sensation
128. free nerve endings	128. response to pain and temperature
129. hair follicle endings	129. touch sensation
130. Krause's end-bulb	130. temperature sensation
131. Meissner's corpuscles	131. touch-pressure sensation
132. Merkel's disk	132. touch-pressure sensation
133. Pacinian corpuscle	133. touch-pressure sensation
134. Ruffini's corpuscle	134. temperature sensation
135. retina	135. visual acuity
136. parathyroid gland	136. calcium balance
137. placenta	137. placental activity
138. skeletal muscle fibers	138. muscle contraction
139. copora cavernosum	139. genital vasodilation
140. corticospinal tract	140. movement control
141. motor cerebral cortex	141. movement control
142. postganglionic neurons	142. control of blood pressure and adrenal activity
143. intramural ganglion	143. distal colon peristalsis
144. hypogastric plexus	144. control of urethral and anal sphincters
145. pelvic plexus	145. genital vasodilatation and penile erection
146. vesical plexus	146. urinary bladder control
147. celiac plexus	147. intestinal peristolisis

- (c) contacting a non-endogenous candidate compound with [a] said endogenous constitutively activated G protein coupled cell surface [orphan] receptor of step (a);

- (d) determining, by measurement of the compound efficacy at said contacted receptor, whether said non-endogenous candidate compound has inverse agonist activity or agonist activity to said receptor of step (a); and
- (e) directly identifying a non-endogenous candidate compound of step [(b)] (d) having inverse agonist activity as an inverse agonist to said receptor of step (a), or having agonist activity as an agonist to said receptor of step (a) [.];
- (f) selecting an inverse agonist to reduce a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a), or selecting an agonist to enhance a selected physiological function of step (b) correlated with the tissue-expression location for said receptor of step (a); and
- (g) contacting said inverse agonist with a mammal comprising said receptor of step (a) and confirming that said inverse agonist reduces said selected physiological function, or contacting said agonist with a mammal comprising said receptor of step (a) and confirming that said agonist enhances said selected physiological function

wherein said directly identified non-endogenous candidate compound of step (e) was not, prior to such direct identification, indirectly identified as an agonist or antagonist to said receptor.

Please add the following new claims:

--45. The method of claim 33 wherein the third intracellular loop of the receptor of step (b) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.--

--46. The method of claim 45 wherein X1 is glycine.--

--47. The method of claim 45 wherein X1 is lysine.--

--48. The method of claim 45 wherein Hy is alanine.--

--49. The method of claim 45 wherein X2 is lysine.--

--50. The method of claim 45 wherein X2 is arginine...--

--51. The method of claim 45 wherein X2 is glutamic acid.--

--52. The method of claim 33 wherein the second intracellular loop of the receptor of step (b) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.--

--53. The method of claim 39 wherein the third intracellular loop of the receptor of step (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.--

--54. The method of claim 53 wherein X1 is glycine.--

--55. The method of claim 53 wherein X1 is lysine.--

--56. The method of claim 53 wherein Hy is alanine.--

--57. The method of claim 53 wherein X2 is lysine.--

--58. The method of claim 53 wherein X2 is arginine.--

--59. The method of claim 53 wherein X2 is glutamic acid.--

--60. The method of claim 39 wherein the second intracellular loop of the receptor of step (a) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.--

--61. The method of claim 45 wherein the sequence X1BBHyX2 is an endogenous sequence.--

--62. The method of claim 52 wherein the sequence XRY is an endogenous sequence.--

--63. The method of claim 33 wherein said mammal of step (h) is a human.--

--64. The method of claim 39 wherein said mammal of step (i) is a human.--

--65. The method of claim 33 wherein said mammal of step (h) is a non-human.--

--66. The method of claim 39 wherein said mammal of step (i) is a non-human.--

--67. The method of claim 33 wherein said physiological function of step (b) is an abnormal physiological function.--

--68. The method of claim 39 wherein said physiological function of step (c) is an abnormal physiological function.--